

Appendix

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: SARAGОВI et al.
Serial number: 10/600,623
Filing date: June 20, 2003
For: COMPOUND TARGETED FOR SPECIFIC CELLS WITH
REDUCED SYSTEMIC TOXICITY
Art Unit: 1642
Examiner: FETTEROLF, Brandon

DECLARATION UNDER 37 C.F.R. SEC. 1.132

I, Uri Saragovi, Ph.D., do hereby declare and state as follows:

1. I received the degrees of B.Sc. in 1984; and Doctor of Philosophy from the University of Miami in 1989. I have more than 24 years of experience and active scientific research activity, and I am an author of numerous scholarly publications as listed in my enclosed *curriculum vitae*.
2. My academic background and experiences in the field of the present invention are listed on the enclosed *curriculum vitae*.
3. I have been a Professor of Pharmacology and of Oncology at McGill University since 1993.
4. I am an inventor in the present application; I have read and am thoroughly familiar with the contents of U.S. Patent Application Serial No. 10/600,623, entitled "COMPOUND TARGETED FOR SPECIFIC CELLS WITH REDUCED SYSTEMIC TOXICITY", including the claims.

5. I have also read and understood the latest Official Action from the PTO dated March 17, 2008. In this Office Action, certain claims (35 and 39) were rejected for obviousness under 35 U.S.C. §103.
6. It is known in the art of tumor therapeutics that several cytotoxic agents such as doxorubicin and paclitaxel are not maximally effective due to the development of multidrug resistance in tumor cells. It is also known that cytotoxic agents such as doxorubicin upregulate the p-glycoprotein pump in tumor cells and this leads to resistance of the tumor cells to the cytotoxic agent.
7. A person of skill in the art would therefore expect that delivering the cytotoxic agent to a tumor cell, such as by using the immunoconjugates described in the present application, would lead to upregulation of the p-glycoprotein pump.
8. Our finding that the p-glycoprotein pump is bypassed in tumor cells when the immunoconjugates described in the present application are administered is therefore surprising and could not have been predicted beforehand by a person of skill in the art.
9. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by a fine or imprisonment, or both (18 U.S.C. Sec. 1001), and may jeopardize the validity of the application of any patent issuing thereon.

Signed

Uri SARAGOV

Dated:

Sept 15, 2008

0

BIOGRAPHICAL SKETCH			
NAME		POSITION TITLE	
H. Uri Saragovi, Ph.D.		Full Professor (tenured) McGill University	
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE	YEARS	FIELD OF STUDY
Brandeis Univ/Florida International Univ	B.Sc.	1984	Biochemistry
University of Miami	PhD	1989	Immunol/Cell & Mol. Biol.
DuPont R&D	Visit. Scient.	1990	Immunotherapeutics
University of Pennsylvania	Post-doct.	1991-93	Receptor & Cancer Biology

A. Positions and Honors

Experience

McGill University. Pharmacology & Therapeutics, Assist. Professor, 1993-1997
 McGill University. Pharmacology & Therapeutics, Associate Professor, 1997 to present
 McGill Cancer Centre, Department of Oncology, Member, 1995 to present
 McGill Cancer Centre, Department of Oncology, Associate Professor, 1997 to present
 McGill Center for Translational Research, Full Member, 1998 to present
 McGill Chemical Biology Program, Full Member, 2002 to present
 Jewish General Hospital-Lady Davis Research Institute. 2003 to present
 Bloomfield Center for Neuroscience, 2003 to present

Editorial Boards

Member of the Editorial Board of "Journal of Biological Chemistry". 2002-2009 (impact factor 7.6)
 Member of the Editorial Board of "Current Medicinal Chemistry - CNS" 2001-2009 (impact factor 5.8)

Member of Grant Review Panels

Cancer Research Society 2006-to date
 National Cancer Institute of Canada. "Growth Factors and Receptors". 2004-2007
 Fundacion de Promoción Científica y Tecnológica de la Republica Argentina (FONCyT). 1999-to date
 Canadian Institute for Health Research. Canada Research Chairs. 2002, 2004
 Canadian Institute for Health Research. Scholar Award Review Committee. 2001-2003
 Canadian Institutes of Health Research, University-Industry Review Committee. 1995-2000.

External and Ad-Hoc Grant Review Panels

Canadian Institutes of Health Research, 2000 - to date.
 Pharmacology, Cancer, Neuroscience, and Biochemistry
 Swiss Government Medical Funding Agency. 2001
 National Institutes of Health (USA), Neuroscience 2000. Also Ad Hoc 2001.
 The Wellcome Trust/Wellcome International, 1999
 National Cancer institute (USA). Site visits for Program Projects. 1999
 Alzheimer's Society

Selected Personal Awards

Monat-Fraser McPherson Award 1993-1995. Agency: McGill University
 Research Scholar Award 1996-2001. Agency: Medical Research Council of Canada /Pharmaceutical Association of Canada (MRC-PMAC).
 Research Scholar Award 2001-2002. Agency: Canadian Institutes of Health Research

B. Selected peer-reviewed publications (in chronological order).

50- Chaohua Yan, Ye Liang, Karen D. Nylander, Judith Wong, Rena M. Rudavsky, H. Uri Saragovi, and Nina Felice Schor. The Trka/p75 ratio determines the mechanism of the anti-apoptotic effect of NGF. (2002). Molec. Pharmacol. 61:710-9.

51- Martin Gagnon and H. Uri Saragovi. Gangliosides: therapeutic agents or therapeutic targets? (2002) Expert Opinion in Therapeutic Patents 12:1215-1223.

- 52- M. Pattarawarapan M.C.Zaccaro **H.U. Saragovi**, and K.Burgess. New Templates for Syntheses of Ring-fused, C¹⁰-Turn Peptidomimetics: Potential TrkA and TrkC Ligands. (2002) J. Med. Chem 45:4387-90.
- 53- **H. Uri Saragovi** and Maria Clara Zaccaro. Small Molecule Peptidomimetic Ligands of Neurotrophin Receptors, Identifying Binding Sites, Activation Sites and Regulatory Sites. Current Pharmaceutical Design, 2002, 8, 99-110 1.
- 54- Naghibalhossaini F, Nault F, **Saragovi U**, Nedev H, Johnstone R. Functional consequences of the in-frame insertion of a transposon into the mutated gamma amino butyric acid transporter of *Saccharomyces cerevisiae*. (2002). Med. Sci. Monit. 8:BR460-70.
- 55- Maryam Taheri, **H. Uri Saragovi**, and Clifford P. Stanners. The Adhesion and differentiation activities of Ig superfamily member CEA can be independently blocked. (2003). J. Biol. Chem 278:14632-9.
- 56- Lubjica Ivanisevic, Kris Banerjee, and **H. Uri Saragovi**. Ligands of p75 regulate a constitutive inhibition of TrkA activation. 2003. Oncogene 22:5677-85.
- 57- Pattarawarapan M, Reyes S, Xia Z, Zaccaro MC, **Saragovi HU**, Burgess K. (2003). Selective formation of homo- and heterobivalent peptidomimetics. J Med Chem. 46:3565-7.
- 58- Songlin Li, **H. Uri Saragovi**, Ronald J. Racine, and Margaret Fahnestock. A ligand of the p65/p95 receptor suppresses perforant path kindling, kindling-induced mossy fiber sprouting, and hilar area changes in adult rats. 2003. Neuroscience 119:1147-56.
- 59- M. Rudzinski Tak-Pan Wong and **H. Uri Saragovi**. Changes in retinal expression of neurotrophins and neurotrophin receptors induced by ocular hypertension. (2004). J Neurobiol. 2004 58:341-54.
- 60- Veronique Guillemard and **H. Uri Saragovi**. Cell surface receptors as therapeutic targets. (2004) Curr Cancer Drug Targets. 4:313-26.
61. Hong Boon Lee, M.C. Zaccaro, M. Pattarawarapan, S. Roy, **H. Uri Saragovi**, and Kevin Burgess. Syntheses and Activities of New C10 beta-Turn Peptidomimetics. 2004. J. Org.Chem. 69:701-13.
- 62- Veronique Guillemard and **H.Uri Saragovi**. Ligand-drug conjugates bypass p-glycoprotein resistance and kill cells selectively in a target-dependent manner *in vitro* and *in vivo*. 2004. Oncogene 23:3613-21.
- 63- M. Bruno, P.B.S. Clarke, A. Seltzer, R. Quirion, A.C. Cuello, and **H. Uri Saragovi**. A small molecule peptidomimetic agonist of TrkA affords a long-lasting improvement of memory and cholinergic deficits in cognitively impaired aged rats. 2004. J. Neurosci. 24:8009-18.
- 64- Counts SE, Nadeem M, Wu J, Ginsberg SD, **Saragovi HU**, Mufson EJ. Reduction of cortical TrkA but not p75(NTR) protein in early-stage Alzheimer's disease. Ann Neurol. 2004. 56:520-31.
- 65- Tyurina YY, Nylander KD, Mirnics ZK, Portugal C, Yan C, Zaccaro C, **Saragovi HU**, Kagan VE, Schor NF. The intracellular domain of p75NTR as a determinant of cellular reducing potential and response to oxidant stress. Aging Cell. 2005 4:187-96.
- 66- Guillemard V, Nedev HN, Berezov A, Murali R, **Saragovi HU**. HER2-mediated internalization of a targeted prodrug cytotoxic conjugate is dependent on the valency of the targeting ligand. DNA Cell Biol. 2005 24:350-8.
- 67- Li S, **Saragovi HU**, Nedev H, Zhao C, Racine RJ, Fahnestock M. Differential actions of nerve growth factor receptors TrkA and p75NTR in a rat model of epileptogenesis. Mol Cell Neurosci. 2005 29:162-72.
- 68- Mirnics ZK, Yan C, Portugal C, Kim TW, **Saragovi HU**, Sisodia SS, Mirnics K, Schor NF. P75 neurotrophin receptor regulates expression of neural cell adhesion molecule 1. Neurobiol Dis. 2005 20(3):969-85.
- 69- Yan C, Mirnics ZK, Portugal CF, Liang Y, Nylander KD, Rudzinski M, Zaccaro C, **Saragovi HU**, Schor NF. Cholesterol biosynthesis and the pro-apoptotic effects of the p75 nerve growth factor receptor in PC12 pheochromocytoma cells. Brain Res Mol Brain Res. 2005; 139(2):225-34.
- 70- M. Rudzinski and **H. Uri Saragovi**. Glaucoma: validated and facile *in vivo* experimental models of a chronic neurodegenerative disease for drug development. 2005. Current Med. Chem. 5:43-49
- 71- Maria Clara Zaccaro, Hong Boon Lee, Mookda Pattarawarapan, Zebin Xia, Antoine Caron, Kevin Burgess, and **H. Uri Saragovi**. SAR of Agonistic Small Molecule Peptidomimetic Ligands of TrkA and

of TrkC Receptors. 2005, Chemistry and Biology. 12(9):1015-28.

72- H. Uri Saragovi. Strategies, Molecular Targets and Animal Models Useful for Developing Therapies for Alzheimer's Disease. 2005. Current Med. Chem. (Editorial) 5:1-3.

73. H. Uri Saragovi. Progression of age-associated cognitive impairment correlates with quantitative and qualitative loss of TrkA receptor protein in NB and cortex. 2005. J. Neurochem. 95(5):1472-80.

74. Hinyu N. Nedev; Guy Klaiman; Andrea LeBlanc, and H. Uri Saragovi. Synthesis and evaluation of novel dipeptidyl benzoyloxymethyl ketones as caspase inhibitors. 2005. Biol. Bioch. Res. Com. 336(2):397-400.

75- Thomas MS, Zhang W, Jordan PM, Saragovi HU, Taglialatela G. Signaling pathways mediating a selective induction of nitric oxide synthase II by tumor necrosis factor alpha in nerve growth factor-responsive cells. J Neuroinflammation. 2005; 6;2:19.

76- Esteban et al. A kinase-deficient TrkC receptor isoform activates ARF6-Rac1 signaling through the scaffold protein Tamalin. 2006. Jour. Cell Biol. In press

77- Ivanisevic, L., and H. Uri Saragovi. "The Neurotrophins". In: Handbook of Biologically Active Peptides. Abba J. Kastin, M.D. Editor-in-Chief. Elsevier (2006, in press)

78- Jennifer Peleshok and H. Uri Saragovi. Functional mimetics of neurotrophins and their receptors. Biochem Soc Trans. 2006, 34:612-7.

79- Ivanisevic L, Zheng W, Woo SB, Neet KE, Saragovi HU. TrkA receptor "hot spots" for binding of NT-3 as a heterologous ligand. J Biol Chem. 2007 Jun 8;282(23):16754-63.

80. Moffett et al. Preparation and Characterization of New Anti-PSMA Monoclonal Antibodies With Potential Clinical Use. Hybridoma (Larchmt). 2007 Dec;26(6):363-72.

81- Angell Y, Chen D, Brahimi F, Saragovi HU, Burgess K. A combinatorial method for solution-phase synthesis of labeled bivalent beta-turn mimics. J Am Chem Soc. In press

82- Shi Z, Birman E, Saragovi HU. Neurotrophic rationale in glaucoma: a TrkA agonist, but not NGF or a p75 antagonist, protects retinal ganglion cells in vivo. Dev Neurobiol. 2007 Jun;67(7):884-94. Erratum in: Dev Neurobiol. 2007 Sep 15;67(11):1547-8.

83- Tomic N, Gosselin M, Wan JF, Saragovi U, Podgorsak EB, Evans M, Devic S. Verification of cell irradiation dose deposition using a radiochromic film. Phys Med Biol. 2007 Jun 7;52(11):3121-31.

84- Lowenthal JW, Malek TR, Saragovi H. Measurement of lymphokine receptors. Curr Protoc Immunol. 2001 May;Chapter 6:Unit 6.1.

85- Moffett S, Mélançon D, DeCrescenzo G, St-Pierre C, Deschênes F, Saragovi HU, Gold P, Cuello AC. Preparation and characterization of new anti-PSMA monoclonal antibodies with potential clinical use. Hybridoma (Larchmt). 2007 Dec;26(6):363-72.

86- Angell Y, Chen D, Brahimi F, Saragovi HU, Burgess K. A combinatorial method for solution-phase synthesis of labeled bivalent beta-turn mimics. J Am Chem Soc. 2008 Jan 16;130(2):556-65.

87- Zhuo YH, Wei YT, Bai YJ, Duan S, Lin MK, Saragovi HU, Ge J. Pro370Leu MYOC gene mutation in a large Chinese family with juvenile-onset open angle glaucoma: correlation between genotype and phenotype. Mol Vis. 2008 Aug 22;14:1533-9.

88- Shi Z, Rudzinski M, Meerovitch K, Lebrun-Julien F, Birman E, Di Polo A, Saragovi HU. alpha 2 macroglobulin is a mediator of retinal ganglion cell death in glaucoma. J Biol Chem. 2008 Aug 13.

PAPERS SUBMITTED

1- Dimerization of a monovalent small molecule ligand changes a TrkA receptor agonist into an antagonist. Fouad Brahimi, Jing Liu, Andrey Malakhov, Shafinaz Chowdhury, Enrico O. Purisima, Ljubica Ivanisevic, Antoine Caron, Kevin Burgess and H. Uri Saragovi. Submitted to: Chemical Biology

2- Differential roles of Trk and p75 neurotrophin receptors in tumorigenesis and chemoresistance ex vivo and in vivo. Muriel Bassili, Nina F. Schor, and H. Uri Saragovi. Submitted to: JPET

3- An agonistic anti-TrkC mAb directed to the juxtamembrane ectodomain defines a functional hot spot interacting with p75 co-receptors. V. Guillemard, L. Ivanisevic, V. Scholten and H. Uri Saragovi. Submitted to: JBC

PATENTS ISSUED

1. Structural analogs of nerve growth factor and their uses. Authors: H. Uri Saragovi, Lynne LeSauter, A.C. Cuello. US patent 6,017,878 (issued Jan 25, 2000)
2. The design of hormone like antibodies with agonistic and antagonistic functions. Authors: H. Uri Saragovi, Lynne LeSauter, Sergei Maliartchouk . WO9521193 (1997) US 6,610,500 B1 (Issued August 26th 2003)
3. Compositions which are immunologically crossreactive with antibodies and preparation methods therefor. Authors: Mark I. Greene, H. Uri Saragovi, and Michael Kahn. US 5,334,702 (Issued August 2, 1994)
4. Beta-turn peptidomimetic ligands of neurotrophin receptors. Authors: H. Uri Saragovi, Kevin Burgess. US filing (1999). 1770-242 PCT. US 10,181,546 (Issued January 2005).
5. Compounds targeted for specific cells, with reduced systemic toxicity. Authors: H. Uri Saragovi, Veronique Guillemard. US filing (2000) 3562-003 PCT
6. Pharmaceutical composition with neurotrophic-like activity. Authors: H. Uri Saragovi, Sergei Maliartchouk. CA2,212,315 (1997); PCT/CA98/00749; EP98938559.6

PATENTS FILED

1. Ligands of Gangliosides and their activity. Authors: H. Uri Saragovi, Martin Gagnon (2002). US Patent Application No. 10/528,542
2. Expression and regulation of pressure-regulated genes in glaucoma. Author: H. Uri Saragovi. US filing (2005).
3. Methods for neuroprotection and selective inhibition of caspases. 2007
4. Ligand-targeted AMF-toxin conjugates for cancer therapeutics (lead applicant Robert Nabi, University of British Columbia). 2008
5. Treatment of glaucoma, 2008. Author: H. Uri Saragovi and Karen Meerovitch
6. Neurotrophin peptidomimetics composition of matter and uses. Authors: H. Uri Saragovi and Kevin Burgess

CURRENT ACTIVE AND PREVIOUS FUNDING (approximate, 5 YEARS)

Chemistry and Biology of GD2 and its ligands. CIHR 2005-2008 (William Lubell co-PI)

Biological response modifiers of neurotrophins and their receptors. CIHR 2004-2009

Novel molecular mechanisms and therapy for glaucoma. CIHR 2003-2006

GD2 therapeutics. CIHR. POP2 program. 2006-2007

CIHR Team Grant in GPCR Allosteric Regulation 2007-2011 (Michel Bouvier co-PI)

Efficacy of TrkA-targeted neuroprotection in Alzheimer's Disease. AHAF-ELAN Partnership 2008-2010

Tumor-targeted therapeutics that overcome drug resistance. Cancer Research Society 2007-2009

NT3 peptidomimetics. NIH 2005-2009

Neurotrophic mechanisms in neuroblastoma. NIH 2005-2009

In vivo PK of a small molecule TrkA peptidomimetic ligand. Alzheimer's Society. 2006-2008

Brain Permeability of peptidomimetics. CIHR. POP1 program. 2004

CONTRACTS & LICENSES (managed by OTT)

Mimetogen Pharmaceuticals Inc

Neubody Inc

ProsCan Pharma Inc